Interrelation Between Electrocardiographic Left Atrial Abnormality, Left Ventricular Hypertrophy, and Mortality in Participants With Hypertension

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Left ventricular hypertrophy (LVH) and left atrial abnormality (LAA) are common correlated complications of hypertension. It is unclear how common for electrocardiographic markers of LAA (ECG-LAA) to coexist with ECG-LVH and how their coexistence impacts their prognostic significance. This analysis included 4,077 participants (61.2 ± 13.0 years, 51.2% women, 48.6% whites) with hypertension from the Third National Health and Nutrition Examination Survey. ECG-LVH was defined by Cornell voltage criteria. ECG-LAA was defined as deep terminal negativity of P wave in V1 >100 μV. Cox proportional hazard analysis was used to examine the associations between various combinations of ECG-LAA and ECG-LVH with all-cause mortality over a median follow-up of 14 years. The baseline prevalence of ECG-LVH, ECG-LAA, and the concomitant presence of both was 3.6%, 2.7%, and 0.34%, respectively. In a multivariable-adjusted model, mortality risk was highest in the group with concomitant ECG-LAA and ECG-LVH (hazard ratio [HR; 95% confidence interval {CI}] 2.69 [1.51, 4.80]), followed by isolated ECG-LAA (HR [95% CI] 1.63 [1.26, 2.12]), and then isolated ECG-LVH (HR [95% CI] 1.40 [1.08, 1.81]), compared with the group without ECG-LAA or ECG-LVH. Effect modification of these results by age and diabetes but not by gender or race was observed. In models with similar adjustment where ECG-LVH and ECG-LAA were entered as 2 separate variables and subsequently additionally adjusted for each other, the mortality risk was essentially unchanged for both variables. In conclusion, in participants with hypertension, ECG-LAA and ECG-LVH are independent markers of poor outcomes, and their concomitant presence carries a higher risk than either marker alone. **(Am J Cardiol 2019;124:886−891)**

Electrocardiographic left atrial (LA) abnormality (ECG-LAA) as determined by abnormal P terminal force in V1 (PTFV1) is a predictor of atrial fibrillation,[1] stroke,[2] congestive heart failure,[3] and including cardiovascular disease (CVD) death.[4] A simplified ECG metric of abnormal PTFV1, deep terminal negativity of P wave in V_1 (DTNPV1), was also independently associated with increased risk of all-cause and CVD mortality and sudden cardiac death (SCD).[5,6] Pathophysiologically, atrial abnormalities on electrocardiogram represent LA pressure overload and are prevalent in participants with hypertension and its complication, including left ventricular dysfunction and left ventricular hypertrophy (LVH).[7–9] LVH is the most common complication of hypertension, a maladaptive response to pressure overload.[10] Electrocardiographic LVH (ECG-LVH) is an established predictor of poor outcomes and has been associated with incident CVD, all-cause mortality, and CVD death.[11] Studies examining the risk of CVD and mortality associated with ECG-LVH and ECG-LAA suggest independent information provided by these markers.[12,13] However, in addition to the limited racial and gender diversity in these studies, detailed analysis of the interrelations between ECG-LVH, ECG-LAA, and outcomes was also lacking. Therefore, we sought to examine the inter-relation between ECG-LAA and ECG-LVH in terms of their association with all-cause mortality in a large multiracial population of men and women free of clinical CVD using data from the Third National Health and Nutrition Examination Survey (NHANES-III).

Methods

NHANES is a periodic survey of the noninstitutionalized civilian population in the United States. Its principal aim is to determine estimates of disease prevalence and health status of children and adults. The structure of the NHANES III (1988 and 1994), its components, and resulting data are published elsewhere.[14] The NHANES III study was approved by the National Center for Health Statistics Research Ethics Review Board, and documented consent was obtained from participants.

For this analysis, we only considered NHANES-III participants who underwent an electrocardiogram (ECG) recording and who were classified as having hypertension per the new

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American College of Cardiology/American Heart Association guidelines (systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥80 mm Hg)[15] or use of antihypertensives. We excluded participants without hypertension, with any rhythm other than sinus or history of CVD (myocardial infarction, heart failure, or stroke). We also excluded participants with poor quality ECGs or with major intraventricular conduction delay (i.e., complete bundle branch blocks and QRS duration ≥120 milliseconds) or with missing mortality data. After exclusions (n = 4,484), 4,077 participants were included in the final analysis.

The 12-lead electrocardiograms at rest were obtained with a Marquette MAC 12 system (Marquette Medical Systems, Milwaukee, Wisconsin) during the mobile examination visits by trained technicians. Analysis of electrocardiograms was achieved through a computerized automated process and visual inspection by a trained technician located in a centralized core laboratory. The amplitude of the terminal negative phase of the P wave in lead V1 was measured automatically. ECG-LAA was defined as DTNPV1 >100 μV.[6] ECG-LVH was defined using Cornell voltage criteria (RaVL and SV3 >2800 μV for men and >2200 μV for women).[16]

The NHANES III participants were followed up for mortality through December 31, 2006. The probabilistic matching method was used to link NHANES III participants with the National Death Index for vital status and the cause of death in deceased participants. Name, social security number, and date of birth were components of 12 identifiers used to match the participants. Follow-up was defined as the interval between the NHANES III examination and either of the following, depending on whichever came first: date of death, date of censoring, or December 31, 2006.

Age, gender, race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, and other), smoking status (never, current, and former), and previous CVD (heart failure, stroke, and coronary heart disease) were self-reported. Blood pressure (mm Hg) was measured while seated, using a standard mercury sphygmomanometer and up to 3 measurements were averaged. Blood samples were analyzed for total cholesterol (TC), triglycerides (TGs), glucose, and so on, using laboratory procedures as reported by National Center for Health Statistics.[14] Diabetes was defined as fasting blood glucose ≥126 mg/dl or use of antidiabetic medications. Hyperlipidemia was defined as any of the following: TC ≥200 mg/dl; TGs ≥150 mg/dl; or by the use of cholesterol-lowering medications. Body mass index was calculated as the weight in kilograms divided by the height in meters squared. Obesity was defined as a body mass index of ≥30 kg/m^2.

Continuous variables were reported as mean ± standard deviation, whereas categorical variables were reported as frequency and percentage. Participants' characteristics were examined and compared across categories stratified by ECG-LAA and ECG-LVH status.

All-cause mortality rates per 1,000 person-year in participants with no ECG-LAA, no ECG-LVH, ECG-LVH, and ECG-LAA in isolation and lastly ECG-LAA and ECG-LVH combined were calculated.

The impact of ECG-LAA and ECG-LVH on each other in terms of their association with all-cause mortality was assessed in 2 ways. First, using multivariable Cox proportional hazard models, we examined the associations between ECG-LAA and ECG-LVH, in isolation and combined, with the risk of mortality. In these models, different combinations of ECG-LAA and ECG-LVH were used as 1 categorical variable with 4 levels as follows: no ECG-LAA or ECG-LVH (reference group), isolated ECG-LAA, isolated ECG-LVH, concomitant ECG-LAA, and ECG-LVH. Second, we examined the risk of mortality associated with ECG-LAA and ECG-LVH when entered separately in 2 separate sets of models, and then when both were entered in the same model as 2 separate variables (i.e., adjusting for each other). This approach aimed to determine how much of the observed risk of mortality associated with ECG-LVH is explained (confounded) by ECG-LAA or vice versa. In both approaches, models were adjusted for demographics (age, gender, and race; model 1), and then adjusted further for diabetes, hyperlipidemia, smoking status, and obesity. The interaction between ECG-LAA and ECG-LVH as predictors for mortality was examined in the multivariable adjusted model (model 2).

As an additional analysis, we investigated the effect modification of risk factors on the association between different combinations of ECG-LAA and ECG-LVH with mortality. To fulfill this aim, we examined the association between different combinations of ECG-LAA and ECG-LVH in subgroups stratified by age (using 65 years as a cut-point), gender, race (whites vs nonwhites), and diabetes. The models were adjusted in a similar fashion to model 2 mentioned previously, and interaction p value was calculated.

All analyses were done using SAS 9.4 (SAS Institute Inc., Cary, North Carolina). Statistical significance was determined as a 2-sided $p < 0.05$.

Results

This analysis included 4,077 participants (61.2 ± 13.0 years, 51.2% women, 48.6% whites). ECG-LAA was present in 2.7% (n = 111) of the participants, of whom 13% had ECG-LVH, whereas ECG-LVH was present in 3.6% (n = 150) of the participants and among those 9% had ECG-LAA.

Table 1 shows participants' characteristics stratified by ECG-LAA absence versus presence and ECG-LVH absence versus presence. Participants with ECG-LAA and ECG-LVH were more likely to be older, females, and have high TC. Participants with ECG-LVH were more likely to be nonwhite, had prevalent diabetes, obesity, and elevated TG levels, but less likely to be ever-smokers. Although participants with ECG-LAA were more likely to be white, had less-prevalent diabetes, obesity, and elevated TGs but more likely to be smokers.

During a median follow-up of approximately 14 years, 1,506 deaths occurred at a rate of 29.3 deaths per 1,000 person-years. The mortality rate was highest among participants with concomitant ECG-LAA and ECG-LVH, followed by isolated ECG-LAA, then ECG-LVH, and was the least among those without ECG-LAA or ECG-LVH (Figure 1).

Table 2 shows the results of Cox proportional hazard analysis where combinations of ECG-LAA and ECG-LVH were used as a 4-level variable (no ECG-LAA or ECG-LVH [reference], concomitant ECG-LAA and ECG-LVH, isolated ECG-LAA, isolated ECG-LVH). In a model adjusted for all potential confounders, compared with no ECG-LAA or ECG-LVH, the risk of mortality was highest in the concomitant ECG-LAA

Table 1
Baseline characteristics of the NHANES-III participants stratified by baseline ECG-LAA and ECG-LVH status

Characteristics	ECG-LAA		p value	ECG-LVH		p value
Mean ± SD or n (%)	Absent (n = 3,966)	Present (n = 111)		Absent (n = 3,927)	Present (n = 150)	
Age (years)	61.0 ± 13.0	66.8 ± 11.4	< .0001	61.1 ± 13.0	64.6 ± 12.5	0.001
Men	1947 (49.0%)	39 (35.1%)	0.003	1949 (49.6%)	37(24.6%)	< .0001
Race			0.03			0.002
Non-Hispanic whites	1927 (48.5%)	58 (52.2%)		1933 (49.2%)	52 (34.6%)	
Non-Hispanic blacks	1001 (25.2%)	37 (33.3%)		987 (25.1%)	51 (34.0%)	
Mexican American	896 (22.5%)	14 (12.6%)		872 (22.2%)	38 (25.3%)	
Others	142 (3.5%)	2 (1.8%)		135 (3.4%)	9 (6.0%)	
Systolic blood pressure (mm Hg)	141.5 ± 17.2	146.7 ± 17.8	0.001	141.1 ± 17.0	154.0 ± 20.9	< .0001
Diastolic blood pressure (mm Hg)	80.1 ± 10.2	80.1 ± 10.8	0.99	80.1 ± 10.1	81.3 ± 13.2	0.27
Antihypertensive medications	1282 (32.3%)	41 (36.9%)	0.30	1255 (31.9%)	68 (45.3%)	0.0006
Diabetes mellitus	508 (12.8%)	13 (11.7%)	0.73	489 (12.4%)	32 (21.3%)	0.001
Antidiabetics	344 (8.6%)	5 (4.5%)	0.12	326 (8.3%)	23 (15.3%)	0.002
Total cholesterol (mg/dl)	221.3 ± 43.5	226.1 ± 44.1	0.27	221.4 ± 43.5	223.7 ± 44.2	0.54
Triglycerides (mg/dl)	169.7 ± 140.7	156.5 ± 109.3	0.22	169.0 ± 139.5	178.0 ± 149.5	0.48
Antihyperlipidemic	138 (3.4%)	2 (1.8%)	0.33	137 (3.4%)	3 (2.0%)	0.32
Obesity	1308 (33.0%)	31 (27.9%)	0.26	1271 (32.3%)	68 (45.3%)	0.0009
Ever smokers	2094 (52.8%)	73 (65.7%)	0.006	2111 (53.7%)	56 (37.3%)	< .0001
ECG-LVH	136 (3.4%)	14 (13%)	< .0001	–	–	–
DTNPV1	–	–	–	97 (2.4%)	14 (9%)	< .0001

DTNPV1 = deep terminal negativity of P wave in V1; ECG-LVH = electrocardiographic left ventricular hypertrophy.
p Value by *t* test for continuous variable or chi-square test for categorical variables.
Obesity defined as body mass index ≥30 kg/m^2.

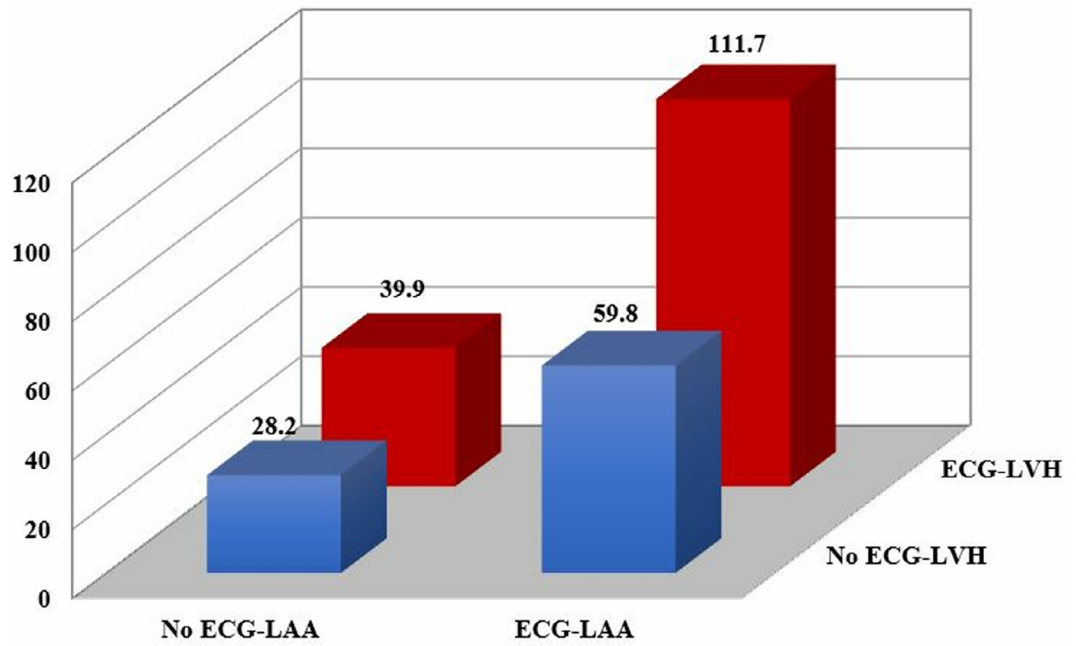

Figure 1. Mortality rates for various combinations of ECG-LAA and ECG-LVH. ECG-LAA = electrocardiographic left atrial abnormality; ECG-LVH = electrocardiographic left ventricular hypertrophy.

and ECG-LVH group (169% increased risk, p < 0.01) followed by isolated ECG-LAA (63% increased risk, p < 0.01), and then isolated ECG-LVH (40% increased risk, p < 0.01; Table 2).

In subgroup analysis, we observed a significant heterogeneity with a stronger association of ECG-LAA and ECG-LVH among young (interaction p value = 0.01) and nondiabetics (interaction p value = 0.03) compared with old, and diabetic participants, respectively (Table 3). There was also a higher risk of mortality among nonwhites compared with whites. However, interaction p value did not reach statistical significance (p = 0.09). No significant interaction was observed by gender (Table 3).

Table 4 shows the risk of mortality associated with each of ECG-LAA and ECG-VH entered separately in different sets of models. As shown, ECG-LAA and ECG-LVH were associated with approximately 1.5 times the risk of mortality in the multivariable adjusted models. The strength of association between ECG-LAA and ECG-LVH with mortality was

Table 2
Association of ECG-LAA and ECG-LVH with all-cause mortality

ECG-LAA	ECG-LVH	Participants	Events	Model 1 HR (95% CI)	p value	Model 2 HR (95% CI)	p value
Absent	Absent	3830	1370 (35.7%)	*Ref*	–	*Ref*	–
Present	Absent	97	61 (62.8%)	1.76 (1.36-2.28)	< .0001	1.63 (1.26-2.12)	0.0002
Absent	Present	136	63 (46.3%)	1.42 (1.10-1.83)	0.006	1.40 (1.08-1.81)	0.009
Present	Present	14	12 (85.7%)	3.35 (1.89-5.94)	< .0001	2.69 (1.51-4.80)	0.0007

CI = confidence interval; ECG-LAA = electrocardiographic left atrial abnormality; ECG-LVH = electrocardiographic left ventricular hypertrophy; HR = hazard ratio.

Model 1 adjusted for age, gender, and race.

Model 2 adjusted for model 1 plus diabetes, smoking, hyperlipidemia, and obesity.

ECG-LAA defined as abnormal deep terminal negativity of P wave in V1.

Table 3
All-cause mortality by ECG-LAA and ECG-LVH status in subgroup analysis

Subgroups	ECG-LAA	ECG-LVH	Participants	Events	HR (95% CI)	Interaction p value
Men	Present	Absent	37	24 (64.8%)	1.71 (1.14-2.58)	0.23
	Absent	Present	35	16 (45.7%)	1.63 (0.99-2.69)	
	Present	Present	2	2 (100%)	9.33 (2.31-37.65)	
Women	Present	Absent	60	37 (61.6%)	1.56 (1.12-2.19)	
	Absent	Present	101	47 (46.5%)	1.32 (0.98-1.79)	
	Present	Present	12	10 (83.3%)	2.33 (1.23-4.42)	
Whites	Present	Absent	52	34 (65.3%)	1.39 (0.98-1.97)	0.09
	Absent	Present	46	26 (56.5%)	1.32 (0.89-1.96)	
	Present	Present	6	6 (100%)	1.53 (0.67-3.49)	
Nonwhites	Present	Absent	45	27 (60.0%)	2.15 (1.46-3.17)	
	Absent	Present	90	37 (41.1%)	1.40 (1.00-1.96)	
	Present	Present	8	6 (75.0%)	5.58 (2.48-12.57)	
≥65 years	Present	Absent	57	45 (78.9%)	1.45 (1.07-1.96)	0.01
	Absent	Present	66	46 (69.7%)	1.47 (1.08-1.99)	
	Present	Present	8	8 (100%)	3.59 (1.78-7.25)	
< 65 years	Present	Absent	40	16 (40.0%)	2.34 (1.41-3.86)	
	Absent	Present	70	17 (24.2%)	1.63 (1.00-2.67)	
	Present	Present	6	4 (66.6%)	8.30 (3.06-22.50)	
Diabetics	Present	Absent	11	6 (54.5%)	0.84 (0.36-1.93)	0.03
	Absent	Present	30	17 (56.6%)	1.02 (0.62-1.70)	
	Present	Present	2	2 (100%)	1.29 (0.30-5.44)	
Nondiabetics	Present	Absent	86	55 (63.9%)	1.84 (1.40-2.42)	
	Absent	Present	106	46 (43.4%)	1.59 (1.18-2.15)	
	Present	Present	12	10 (83.3%)	4.03 (2.15-7.54)	

CI = confidence interval; ECG-LAA = electrocardiographic left atrial abnormality; ECG-LVH = electrocardiographic left ventricular hypertrophy; HR = hazard ratio.

Model adjusted for age, gender, race, diabetes, smoking, hyperlipidemia, and obesity.

ECG-LAA defined as abnormal deep terminal negativity of P wave in V1.

Table 4
Mortality risk associated with ECG-LVH and ECG-LAA with or without adjustment for each other

	Model 1 HR (95% CI)	p value	Model 2 HR (95% CI)	p value
ECG-LVH	1.53 (1.21-1.94)	0.0003	1.49 (1.17-1.88)	0.0009
ECG-LVH *with additional adjustment for ECG-LAA*	1.48 (1.16-1.87)	0.001	1.43 (1.13-1.82)	0.002
ECG-LAA	1.88 (1.48-2.38)	< .0001	1.72 (1.35-2.18)	< .0001
ECG-LAA *with additional adjustment for ECG-LVH*	1.83 (1.44-2.32)	< .0001	1.67 (1.31-2.12)	< .0001

CI = confidence interval; ECG-LAA = electrocardiographic left atrial abnormality; ECG-LVH = electrocardiographic left ventricular hypertrophy; HR = hazard ratio.

Model 1 adjusted for age, gender, and race.

Model 2 adjusted for model 1 plus diabetes, smoking, hyperlipidemia, and obesity.

ECG-LAA defined as abnormal deep terminal negativity of P wave in V1.

not significantly attenuated when both were entered in the same model as 2 separate variables (Table 4). There was no significant interaction between ECG-LAA and ECG-LVH as predictors for mortality (interaction p = 0.68).

Discussion

In this analysis from NHANES-III, we examined the interrelation between ECG-LAA and ECG-LVH in NHANES participants with hypertension who were free of CVD at baseline.

The main findings are as follows: first, ECG-LAA was associated with increased risk of mortality even after adjustment for ECG-LVH and ECG-LVH was associated with increased risk of mortality even after adjustment for ECG-LAA; second, concomitant presence of ECG-LAA and ECG-LVH carried more risk of mortality than the presence of each in isolation; third, the mortality risk with concomitant presence of ECG-LAA and ECG-LVH was stronger in young and nondiabetic compared with old and diabetic participants, respectively. These findings suggest that ECG-LAA and ECG-LVH are 2 independent predictors of mortality and the prognostic significance of one does not depend or explained by the other but when present together confers additional prognostic value in predicting poor outcomes. The increased morbidity and mortality associated with hypertension and heterogeneity in the risk of outcomes among those with hypertension require looking for new markers such as ECG-LAA and ECG-LVH that may help identify those at high risk for future complications.

P-wave indices especially abnormal PTFV1 that is the product of amplitude and duration of the negative terminal portion of the P wave in V1 and DTNPV1 are markers of impaired interatrial conduction due to LA abnormalities.[17] However, ECG-LAA not only represents structural and electrical remodeling but also reflects impaired LA function. In a study by Tiffany et al,[18] a significant association of P-primer amplitude in V1 or DTNPV1 with LA minimal volume index, global LA ejection fraction (LAEF), and LA reservoir function characterized it as a marker of LA dysfunction, which, in turn, can signify the presence of LV diastolic dysfunction. Moreover, in patients with mitral stenosis, commissurotomy has been shown to reduce both LA pressures and volumes, resulting in decreased P-wave duration on ECG.[19] Thus, ECG indices of LA abnormality represent LA tissue substrate, geometry, and loading conditions, with P-wave morphology representing a complex index for LA arrhythmic substrate.[20]

ECG-LAA, as determined by DTNPV1, is also a marker of LV fibrosis even before any enlargement or functional impairment of LA and systolic or diastolic dysfunction of LV. But as the LA function impairs or LA enlarges, so is the deepening of p-prime amplitude in V1.[18] A strong association of ECG-LAA determined by DTNPV1 with SCD further support that DTNPV1 is an intermediate marker on the pathway linking cardiac fibrosis with atrial and ventricular arrhythmia and SCD.[6] In a study of participants with mild congestive heart failure by Baturova et al,[21] benefits of cardiac resynchronization in patient with left bundle branch block (LBBB) were only demonstrated in those with normal PTFV1, whereas participants with LBBB and abnormal PTFV1 had similar prognosis as participants treated with ICD and without LBBB, thus indicating that presence of abnormal PTFV1 may be a marker of advanced remodeling stages and these participants unlikely to benefit from CRT.

ECG-LVH is predictive of cardiovascular CVD events, and all-cause mortality, and this risk remains elevated even after adjustment for echo-LVH, suggesting that ECG-LVH reflects changes due to a combination of anatomical and electrophysiological remodeling in hypertrophied heart than provided by LV mass alone.[22] A regression of ECG-LVH with antihypertensive treatment was associated with a reduction of the composite outcome of CVD events and CVD death independent of blood pressure changes.[23]

In subgroup analysis, we observed a strong association of concomitant ECG-LAA and ECG-LVH with mortality among younger participants compared with older participants. Interestingly, we observed a strong association of nondiabetics with all-cause mortality in the presence of ECG-LVH and ECG-LAA, even though the prevalence of ECG-LVH is higher in diabetes.[24] Exclusion of participants with prevalent CVD in our sample who may have had already experienced the deleterious effect of diabetes could have resulted in attenuation of association of diabetes with mortality in the subgroup with ECG-LVH and ECG-LAA. However, this argument is just speculation and actual reasons for such heterogeneity are unclear.

LA enlargement is commonly found independent of the presence of other echocardiographic signs of hypertensive heart disease like concentric LVH or LVH remodeling,[25] so, coexistence of ECG-LAA and ECG-LVH likely represents advanced structural and electrical remodeling.[12,13] Despite the low sensitivity of ECG for detecting LVH and LA dilatation,[26,27] each is independently predictive of mortality. The highest risk of mortality associated with their concomitant presence suggests that additional prognostic information can be obtained from ECG to identify high-risk populations.

As regression of ECG-LVH is associated with reduction of CVD outcomes and mortality, future studies should also screen patients for the presence of DTNPV1 and if present, aggressive lifestyle modification and target therapies can potentially decrease LV pressure and thus decrease LV volume/pressure, can possibly induce regression of DTNPV1, and may result in reduction of poor outcomes. ECG is a widely available tool and can be used at the population level for risk stratification and in clinical trials, DTNPV1, as a marker of preclinical CVD, can be used as an end point to assess the efficacy of future antifibrotic and antihypertensive treatments,[28] thus increasing the power and reducing the cost of the trial. However, future large studies are needed to test this hypothesis.

Our results should be read in the context of certain limitations. We lack data on echocardiography, which can measure accurately LV mass and LA dilatation. However, we aimed to explore interrelation with ECG-LAA and ECG-LVH as markers of electrophysiological remodeling. Despite the low sensitivity of ECG in detecting LV mass and LA dilatation, it captures electrophysiological remodeling due to LA structural and functional abnormalities as well as due to increased LV mass, respectively,[26,29] which may not be captured by echocardiogram.[30] Although we

have adjusted for potential confounders, residual confounding remains a possibility in all analyses, another limitation of our study. Finally, as NHANES-III lacks information on valvular heart disease, we are unable to take into account the potential impact of valvular heart disease on ECG-LAA or ECG-LVH. Strengths of our study include its large sample size, community-based and multiracial population, and a representative sampling of the US population. Also, our data included well-ascertained variables and outcomes, including ECG data evaluated at a central reading center.

Disclosures

The authors have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.06.003.

1. Soliman EZ, Prineas RJ, Case LD, Zhang ZM, Goff DC Jr. Ethnic distribution of ECG predictors of atrial fibrillation and its impact on understanding the ethnic distribution of ischemic stroke in the Atherosclerosis Risk in Communities (ARIC) study. *Stroke* 2009;40:1204–1211.
2. Kamel H, O'Neal WT, Okin PM, Loehr LR, Alonso A, Soliman EZ. Electrocardiographic left atrial abnormality and stroke subtype in the atherosclerosis risk in communities study. *Ann Neurol* 2015;78:670–678.
3. Ariyarajah V, Malinski M, Zieroth S, Harizi R, Morris A, Spodick DH. Risk stratification for recurrent heart failure in patients post-myocardial infarction with electrocardiographic and echocardiographic left atrial abnormality. *Am J Cardiol* 2008;101:1373–1378.
4. Eranti A, Aro AL, Kerola T, Anttonen O, Rissanen HA, Tikkanen JT, Junttila MJ, Kentta TV, Knekt P, Huikuri HV. Prevalence and prognostic significance of abnormal P terminal force in lead V1 of the ECG in the general population. *Circ Arrhythm Electrophysiol* 2014;7:1116–1121.
5. Tereshchenko LG, Shah AJ, Li Y, Soliman EZ. Electrocardiographic deep terminal negativity of the P wave in V1 and risk of mortality: the National Health and Nutrition Examination Survey III. *J Cardiovasc Electrophysiol* 2014;25:1242–1248.
6. Tereshchenko LG, Henrikson CA, Sotoodehnia N, Arking DE, Agarwal SK, Siscovick DS, Post WS, Solomon SD, Coresh J, Josephson ME, Soliman EZ. Electrocardiographic deep terminal negativity of the P wave in V(1) and risk of sudden cardiac death: the Atherosclerosis Risk in Communities (ARIC) study. *J Am Heart Assoc* 2014;3:e001387.
7. Shimizu M, Nakagawa K, Nishida N, Kashiro S, Hirata S, Okada M, Ishikawa K. V1P-terminal force evaluated by left ventricular inflow velocity patterns in pulsed Doppler echocardiography. *J Cardiol* 1987;17:341–352.
8. Recke SH, Esperer HD, Eberlein U, von der Emde J, Gansser R. Electrocardiographic markers of impaired left ventricular ejection performance in aortic stenosis. *J Electrocardiol* 1989;22:45–52.
9. Chen LY, Bigger JT, Hickey KT, Chen H, Lopez-Jimenez C, Banerji MA, Evans G, Fleg JL, Papademetriou V, Thomas A, Woo V, Seaquist ER, Soliman EZ. Effect of intensive blood pressure lowering on incident atrial fibrillation and P-wave indices in the ACCORD blood pressure trial. *Am J Hypertens* 2016;29:1276–1282.
10. Katholi RE, Couri DM. Left ventricular hypertrophy: major risk factor in patients with hypertension: update and practical clinical applications. *Int J Hypertens* 2011;2011:495349.
11. Soliman EZ, Shah AJ, Boerkircher A, Li Y, Rautaharju PM. Inter-relationship between electrocardiographic left ventricular hypertrophy and QT prolongation as predictors of increased risk of mortality in the general population. *Circ Arrhythm Electrophysiol* 2014;7:400–406.
12. Pirinen J, Eranti A, Knekt P, Lehto M, Martinez-Majander N, Aro AL, Rissanen H, Heliovaara M, Kaste M, Tatlisumak T, Huikuri H, Putaala J. ECG markers associated with ischemic stroke at young age—a case-control study. *Ann Med* 2017;49:562–568.
13. Hsieh BP, Pham MX, Froelicher VF. Prognostic value of electrocardiographic criteria for left ventricular hypertrophy. *Am Heart J* 2005;150:161–167.
14. Plan and operation of the Third National Health and Nutrition Examination Survey, 1988-94. Series 1: programs and collection procedures. *Vital Health Stat 1* 1994:1–407.
15. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbiagele B, Smith SC Jr, Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA Sr, Williamson JD, Wright JT Jr. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. *Hypertension* 2018;71:e13–e115.
16. Casale PN, Devereux RB, Kligfield P, Eisenberg RR, Miller DH, Chaudhary BS, Phillips MC. Electrocardiographic detection of left ventricular hypertrophy: development and prospective validation of improved criteria. *J Am Coll Cardiol* 1985;6:572–580.
17. Josephson ME, Kastor JA, Morganroth J. Electrocardiographic left atrial enlargement. Electrophysiologic, echocardiographic and hemodynamic correlates. *Am J Cardiol* 1977;39:967–971.
18. Tiffany Win T, Ambale Venkatesh B, Volpe GJ, Mewton N, Rizzi P, Sharma RK, Strauss DG, Lima JA, Tereshchenko LG. Associations of electrocardiographic P-wave characteristics with left atrial function, and diffuse left ventricular fibrosis defined by cardiac magnetic resonance: the PRIMERI study. *Heart Rhythm* 2015;12:155–162.
19. John B, Stiles MK, Kuklik P, Brooks AG, Chandy ST, Kalman JM, Sanders P. Reverse remodeling of the atria after treatment of chronic stretch in humans: implications for the atrial fibrillation substrate. *J Am Coll Cardiol* 2010;55:1217–1226.
20. Weinsaft JW, Kochav JD, Kim J, Gurevich S, Volo SC, Afroz A, Petashnick M, Kim A, Devereux RB, Okin PM. P wave area for quantitative electrocardiographic assessment of left atrial remodeling. *PLoS One* 2014;9:e99178.
21. Baturova MA, Kutyifa V, McNitt S, Polonsky B, Solomon S, Carlson J, Zareba W, Platonov PG. Usefulness of electrocardiographic left atrial abnormality to predict response to cardiac resynchronization therapy in patients with mild heart failure and left bundle branch block (a multicenter automatic defibrillator implantation trial with cardiac resynchronization therapy substudy). *Am J Cardiol* 2018;122:268–274.
22. Leigh JA, O'Neal WT, Soliman EZ. Electrocardiographic left ventricular hypertrophy as a predictor of cardiovascular disease independent of left ventricular anatomy in subjects aged ≥65 years. *Am J Cardiol* 2016;117:1831–1835.
23. Okin PM, Devereux RB, Jern S, Kjeldsen SE, Julius S, Nieminen MS, Snapinn S, Harris KE, Aurup P, Edelman JM, Wedel H, Lindholm LH, Dahlof B. Regression of electrocardiographic left ventricular hypertrophy during antihypertensive treatment and the prediction of major cardiovascular events. *JAMA* 2004;292:2343–2349.
24. Eguchi K, Boden-Albala B, Jin Z, Rundek T, Sacco RL, Homma S, Di Tullio MR. Association between diabetes mellitus and left ventricular hypertrophy in a multiethnic population. *Am J Cardiol* 2008;101:1787–1791.
25. Milan A, Puglisi E, Magnino C, Naso D, Abram S, Avenatti E, Rabbia F, Mulatero P, Veglio F. Left atrial enlargement in essential hypertension: role in the assessment of subclinical hypertensive heart disease. *Blood Press* 2012;21:88–96.
26. Bacharova L, Chen H, Estes EH, Mateasik A, Bluemke DA, Lima JA, Burke GL, Soliman EZ. Determinants of discrepancies in detection and comparison of the prognostic significance of left ventricular hypertrophy by electrocardiogram and cardiac magnetic resonance imaging. *Am J Cardiol* 2015;115:515–522.
27. Munuswamy K, Alpert MA, Martin RH, Whiting RB, Mechlin NJ. Sensitivity and specificity of commonly used electrocardiographic criteria for left atrial enlargement determined by M-mode echocardiography. *Am J Cardiol* 1984;53:829–832.
28. Komatsu T, Ozawa M, Tachibana H, Sato Y, Orii M, Kunugida F, Nakamura M. Combination therapy with amiodarone and enalapril in patients with paroxysmal atrial fibrillation prevents the development of structural atrial remodeling. *Int Heart J* 2008;49:435–447.
29. Okreglicki AM. P terminal force in lead V (1). *Am J Cardiol* 2000;86:255.
30. Kohsaka S, Sciacca RR, Sugioka K, Sacco RL, Homma S, Di Tullio MR. Electrocardiographic left atrial abnormalities and risk of ischemic stroke. *Stroke* 2005;36:2481–2483.